Thyroid Hormone in the Pediatric Intensive Care Unit

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Abstract

Thyroid hormones are key factors necessary for normal growth and development in children. They have tight control of metabolic rate and, as a result, frequently become altered in their synthesis and/or release during times of stress or critical illness. Disturbances in thyroid hormone homeostasis have been well described in several pathologic states, including sepsis/septic shock, renal failure, trauma, severe malnutrition, and following cardiopulmonary bypass. Specifically, a decrease in serum triiodothyronine (T_3) and a concomitant increase in reverse triiodothyronine (rT_3) levels are the most common changes observed. It is further noteworthy that serum thyroxine (T_4), rT_3, and T_3 levels change in relation to severity of nonthyroidal illness. Many past investigators have speculated that these alterations are a teleological adaptation to severe illness and the increased metabolic demands that critical illness bears. However, this paradigm has been challenged through multiple avenues and has lost support over the past few years. Instead the "inflammatory hypothesis" has emerged implicating a cytokine surge as the mediator of thyroid hormone disruption. Overall, the demonstrated association between low thyroid hormone levels and poor clinical outcomes, the beneficial effects of thyroid hormone supplementation in multiple critically ill subpopulations, and the well-established safety profile of T_3 therapy make thyroid hormone supplementation in the pediatric ICU worth consideration.

Keywords
- thyroid hormone
- critical illness
- neuroendocrine

Introduction

The prevalence of neuroendocrine dysfunction in the setting of critical illness has been widely documented.[1] The initial response to acute insults, such as systemic infection, trauma, and cardiac surgery, results in an increased availability of glucose, amino acids, and free fatty acids. Paradoxically, use of these substrates is reduced and directed toward maintenance of vital organ function. The acute metabolic response is a direct result of endocrine changes, including activation of the hypothalamic-pituitary-adrenocortical axis as well as perturbations in the production/secretion of vasopressin, B-type natriuretic peptide (BNP), prolactin and growth hormone, and insulin-like growth factor as well as thyroid hormone.[2] Going a step further, multiple studies have demonstrated strong associations between the degree of these endocrine perturbations and severity of illness in adults.[3] The data in pediatrics in this field are sparse relative to that in the adult population. The challenges faced when defining the endocrine response to critical illness in the pediatric population include differences in age/development, small study sample sizes, intensive care unit (ICU) population heterogeneity, and differing definitions of endocrine "deficiencies."

Disturbances in thyroid hormone homeostasis have been well described in several pathologic states, including sepsis/septic shock, renal failure, trauma, severe malnutrition, and following cardiopulmonary bypass (CPB).[4–7] Low-circulating thyroid hormone levels observed in these states are associated with worse clinical outcomes. A long-held paradigm includes the theory that these low thyroid syndromes represent adaptive responses, which reduce metabolic demand and inhibit anabolism during periods of stress. However,

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recent clinical trials have shown positive responses to thyroid hormone supplementation during specific pathologic states.[8,9] In particular, results from the TRICC (Triiodothyronine Supplementation in Infants and Children undergoing Cardiopulmonary Bypass) have challenged this paradigm.[10]

In this article, we review the data in pediatrics demonstrating thyroid function in the setting of various disease states as well as clinical outcomes following thyroid hormone supplementation in pediatric critical illness.

Normal Physiology

Thyroid hormones are key factors necessary for normal growth and development in children. They have tight control of metabolic rate and, as a result, frequently become altered in their synthesis and/or release during times of stress or critical illness. Thyroid hormone is tightly controlled by a classic feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus, stimulating synthesis, and release of thyroid-stimulating hormone (TSH) from the pituitary gland. In turn, TSH signals the thyroid gland to synthesize and secrete thyroid hormones (thyroxine, T_4; triiodothyronine, T_3). In normal conditions, 100% of T_4 and 10 to 20% of T_3 are secreted from the thyroid gland to the serum. Once in the serum, T_4 is converted to T_3 via peripheral monodeiodination by the enzyme 5′-monodeiodinase in the liver and kidney. Circulating T_3 and T_4 inhibit release of both TRH and TSH. T_4 can also be converted to reverse T_3 (rT_3), which is more or less metabolically inactive, by 5′-monodeiodinase. Thyroid hormones are primarily bound to carrier proteins in the serum (thyroxine-binding globulin [TBG], prealbumin, and albumin). However, the free hormone is the metabolically active form, capable of causing both nongenomic (immediate) effects at multiple sites as well as genomic (delayed) effects via modulation of gene transcription and protein translation.[11]

Critical Nonthyroidal Illness

Serum thyroid hormone levels decrease in various disease states. Specifically, a decrease in serum T_3 and a concomitant increase in rT_3 levels are the most common changes observed.[12] Of note, in nonthyroidal illness, serum T_4, rT_3, and T_3 levels change in relation to severity of disease.[3,13] In mild disease, there is a reduction in circulating T_3, increase in serum rT_3, and no change in serum-free T_4, total T_4, or TSH. In moderate disease, there is a slight increase in free T_4 and a further decrease in T_3 and increase in rT_3. In severe disease, there is a loss of pulsatile secretion of TSH, decrease in T_4, T_3, and free T_4, and an increase followed by a decrease in rT_3.[12,14] As alluded to in the introduction, many past investigators have speculated that these alterations are a teleological adaptation to severe illness and the increased metabolic demands that critical illness bears.[1] However, this paradigm has been challenged through multiple avenues and has lost support over the past few years.

The inflammatory hypothesis implicating a cytokine surge as mediator of thyroid hormone disruption has emerged over the past decade (►**Fig. 1**). The mechanism of inflammatory response in critical illness has been reviewed in detail elsewhere.[15] However, local and systemic cytokine releases occur in response to stress and/or foreign invasion, and are mediated by both innate and adaptive immunity. Experiments performed in cell culture milieu, in vivo, and in the clinical setting have implicated a role for inflammatory modulation of thyroid hormone homeostasis during critical illness. Specific cytokines appear to modulate the thyroid hormone axis at multiple levels. For instance, Yu and Koenig and Nagaya et al have shown that cytokines modulate the final conversion of T_4 to active T_3.[16,17] Using cultured hepatocytes, both groups demonstrated that various inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α)–activated nuclear factor-κB (NF-κB), interfere with T_3-promoted transcription of 5′-deiodinase, which metabolizes the T_4 to T_3 conversion. Thus, these interleukins inhibit the normal positive feedback loop promoting this conversion. Other studies show inhibition of thyroid hormone axis by various inflammatory cytokines at different levels including end-organ response to T_3.[18–20] The latter involves predominantly cytokine interaction or competition with T_3, which affects binding of thyroid receptor or coreceptors at DNA-binding sites[21]

Multiple investigators have examined the interactions between cytokines and thyroid hormone homeostasis in healthy subjects.[15] Studies have produced seemingly conflicting results, likely due to the inconsistency in the cytokine delivery, dose, and timing. For example, Stouthard et al were unable to produce nonthyroidal illness with the administration of cytokines to healthy subjects.[19] Likewise, van der Poll et al were unable to reverse endotoxemia-induced nonthyroidal illness induced through cytokine antagonism.[22] On the other hand, Torpy and colleagues observed a 19% higher T_3 level and a significant elevation of T_4 levels 24 hours after IL-6 administration to healthy subjects. They concluded that the IL-6–induced thyroid dysfunction was due either to inhibition of T_4 degradation at the liver by type 1 5′-deiodinase, direct action of IL-6 on the thyroid gland, or both.[23]

Studying the effects of another cytokine (TNF-α), they found that TNF-α administration to healthy patients resulted in a decrease in serum T_3 and an increase in serum rT_3.[17] Unlike IL-6, this work failed to demonstrate a relationship between serum TNF-α levels and thyroid parameters. Based on these findings, the authors concluded that the role of TNF-α is indirect, exerting its effects on IL-6 directly, thereby leading to thyroid dysfunction.[24,25] Furthermore, an association between TNF- α and leptin has been demonstrated among patients with nonthyroidal illness syndrome in the setting of chronic obstructive pulmonary disease and ankylosing spondylitis. While further studies are needed, the authors concluded that it is possible that leptin alters the set point for feedback sensitivity of TRH producing neurons of the hypothalamic-pituitary-thyroid axis.[26–28]

Further data supporting the hypothesis that circulating cytokines suppress thyroid hormone levels in children have been provided by Priest and colleagues. They investigated the relationship between circulating T_3 and multiple cytokines using multiplex technology. Of the eight cytokines evaluated,

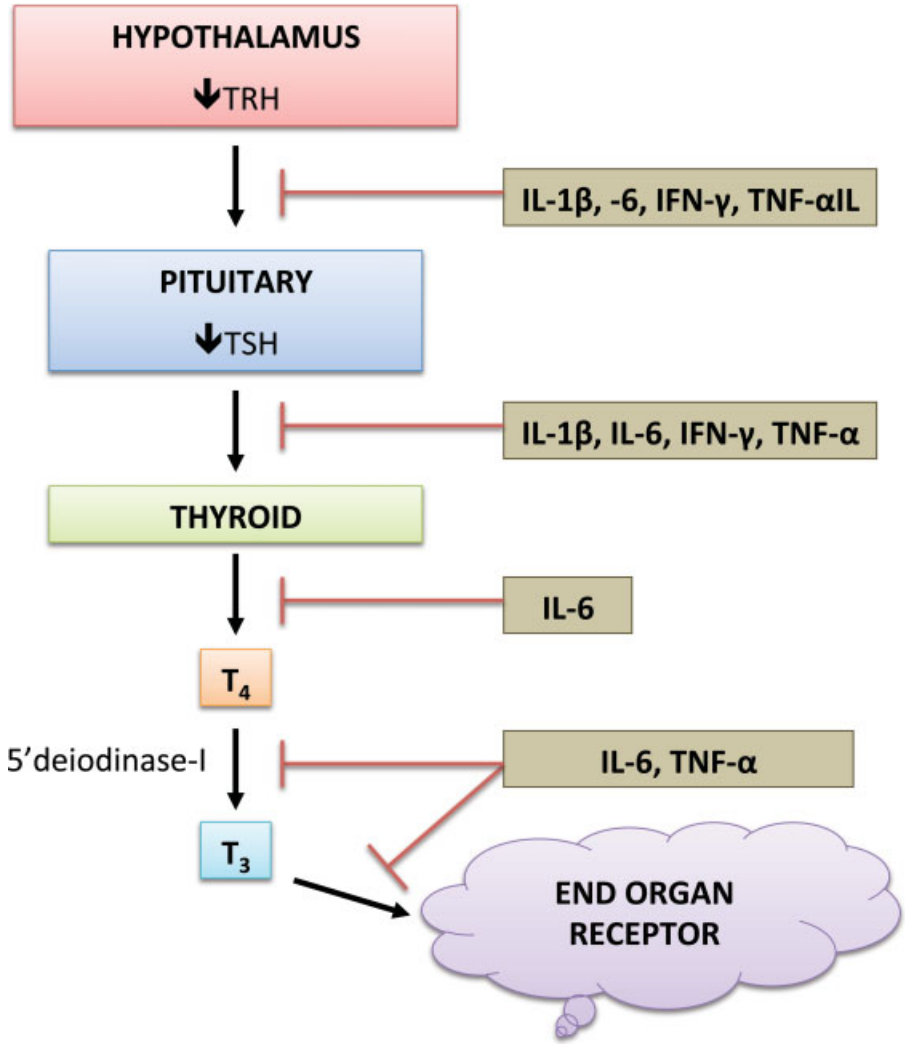

Fig. 1 Cytokine-mediated decrease in production/secretion of TRH and TSH as well as peripheral conversion of T_4 to active T_3. T_4, thyroxine; T_3, triiodothyronine; IFN, interferon; IL, interleukin; MIF, macrophage-inhibiting factor TNF, tumor necrosis factor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

IL-1B showed the most significant and tightly linked relationship to T_3. Surprisingly, T_3 levels related inversely to IL-1B even prior to the initiation of CPB. Furthermore, this inverse relationship held postoperatively up to 72 hours. Taken all together, there are substantial data from multiple avenues of investigation supporting a mechanism for inflammatory mediated suppression of the thyroid hormone axis.

In addition to critical illness leading to low thyroid levels, ICU patients are at risk for exposure to other factors, which may cause or exacerbate depression of circulating thyroid hormone levels. Many common ICU medications increase thyroid hormone metabolism (phenobarbital, rifampin, phenytoin), decrease thyroid hormone secretion (amiodarone, lithium), decrease TSH secretion (dopamine, glucocorticoids, octreotide), and decrease thyroid hormone absorption (ferrous sulfate, aluminum hydroxide, sucralfate).[12] Last, exposure to CPB, particularly in newborns, represents one of the most profound effectors of thyroid hormone levels (see as follows).

Cantinotti and colleagues provided detailed age-related data in patient cohorts undergoing CPB. They demonstrated that circulating thyroid hormone response in neonates differed substantially from older age groups, including infants (30 days to 1 year), and older children. Postoperatively, neonates had prolonged reductions in TSH compared with children, reaching a nadir at 36 hours and remaining depressed for as long as 100+ hours. The ultimate recovery of these levels was quite slow in neonates, whereas older children showed prompt recovery. Furthermore, TSH nadir emerged as a significant predictor of TTE after surgery in the neonatal multivariate model but not that performed in older children, making the observed age differences in TSH response following bypass clinically relevant.[29]

Thyroid Dysfunction in Sepsis/Septic Shock

Sepsis, likely because of systemic inflammatory response, also disturbs thyroid hormone homeostasis. In particular,

early sepsis inhibits T_4 conversion to T_3 which is manifested by low T_3 will relatively normal TSH and T_4 levels.[30] Recent large retrospective studies in septic adults have shown associations between thyroid hormone levels and clinical outcomes. For example, Meyer et al showed that sepsis nonsurvivors had lower T_3 and free T_4 levels compared with survivors on the day of death. However, thyroid hormone levels at admission were not prognostic.[31] Furthermore, both these studies indicated that declination in T_4 suggested poor prognosis.

Associations between sepsis and thyroid dysfunction also appear in pediatric reports. A large epidemiological study showed that maternal primary or "iatrogenic" hypothyroidism posed a significant risk factor for neonatal sepsis and admission to the neonatal intensive care unit.[32] Joosten and colleagues published a cohort study of children presenting with meningococcal sepsis, demonstrating that both survivors and nonsurvivors demonstrated signs of nonthyroidal illness with abnormally low serum T_4 and T_3 as well as high rT_3 levels during their ICU admission. Furthermore, there was a significant difference between survivors and nonsurvivors in mean T_3 (0.53 vs. 0.38 nmol/L) and rT_3 (0.75 vs. 1.44 nmol/L). In those who survived, there was a significant decrease of rT_3 levels and an increase in the T_3/rT_3 ratio within 48 hours of ICU admission.[20] These findings were supported by later work published by Yildizdas et al, who found that total T_3, free T_3, total T_4, and free T_4 were markedly lower in children with bacterial sepsis and/or septic shock when compared with age- and sex-matched, healthy controls. Further, among those with sepsis/septic shock, these levels were significantly lower in nonsurvivors compared with survivors.[33]

Joosten published a follow-up study with den Brinker and colleagues demonstrating that all children presenting with meningococcal septic shock showed signs of sick euthyroid syndrome. Specifically, they all had low total T_3, and high rT_3 without compensatory elevated TSH. Moreover, changes in thyroid parameters within the first 24 hours were related to pediatric intensive care unit (PICU) length of stay. Interestingly, in children receiving dopamine, TSH and T_3/rT_3 ratios remained unchanged, whereas both values increased in those who did not receive dopamine or in whom dopamine was discontinued.[6]

den Brinker and colleagues went on to publish work focusing only on the non–dopamine-treated children from their previous study. They found that T_4 and TBG levels declined with increasing disease severity and that TBG levels inversely correlated with elastase levels. They concluded that lower T_4 levels were related to increased TBG turnover by elastase. Further, the T_3/rT_3 ratio and T_4 levels were predictive of mortality.[6] Lodha et al found a similar pattern in thyroid hormone derangements in a prospective cohort study of children with sepsis and septic shock. Although they found lower levels of T_3, T_4, free T_3, and free T_4 in patients diagnosed with septic shock versus sepsis, contrary to den Brinker's findings, there was no significant difference in levels between the survival and death groups.[34] However, the study does not provide clarity regarding when thyroid levels were obtained within the disease course, and serial levels were not performed.

Thyroid Dysfunction with Mechanical Circulatory Support

Multiple studies have described the transient decline in serum thyroid hormone concentrations following CPB. In 2000, Bettendorf and colleagues performed a randomized, double-blind, placebo-controlled trial in which 40 children were assigned either placebo or a daily infusion of T_4 postoperatively for up to 12 days. Similar to findings in the sepsis/septic shock population, all postoperative patients had low plasma concentrations of T_4, free T_4, and T_3 as well as high levels of rT_3. Following treatment with T_3, plasma T_3 levels were significantly higher and systolic cardiac function was significantly improved compared with placebo (mean change in cardiac index: 20.4 vs. 10.0%). Last, treatment with T_3 was found to reduce postoperative intensive care as measured by the therapeutic intervention scoring system.[35] This study used an extremely wide range of patient ages as well as cardiac surgical complexity.

Based on the clinical studies by Bettendorf et al, research by other groups further demonstrated improved cardiac function with thyroid hormone supplementation. For example, Danzi and colleagues performed a study to investigate the underlying mechanism of this improvement. Specifically, they evaluated gene transcription for three cardiac proteins (adenine nucleotide translocator isoform-1 [ANT-1], α-myosin heavy chain [α-MHC], and sodium calcium exchanger-1 [NCX-1]) to test the hypothesis that T_3 mediates gene transcription in the hearts of infants during CPB. ANT-1, the gene regulating the mitochondrial protein that controls adenosine diphosphate/ATP exchange, was upregulated in infant myocardial biopsy specimens that received T_3 supplementation. This study highlights the importance of delayed, transcriptionally mediated action of T_3.[11] These actions are separate from the nongenomic mechanisms of thyroid hormone, which occur at the cell membrane and are immediate. These actions include rapid T_3-mediated sodium influx stimulation, thereby indirectly increasing intracellular calcium via sodium-calcium exchange, leading to positive inotropic effects.[8]

The same group, in collaboration with other investigators, went on to publish the TRICC multicenter, double-blind, placebo-controlled randomized trial in children younger than 2 years undergoing heart surgery utilizing CPB. This study tested the hypothesis that T_3 supplementation is safe and that it produces significant improvements in postoperative clinical outcomes. They found that time to extubation (TTE), the primary clinical outcome measure, did not differ between treatment groups. However, in children younger than 5 months, randomization to the T_3 treatment arm resulted in significantly shorter median TTE compared with the placebo group (55 vs. 98 hours, 95% confidence interval [CI]: 71–142). The clinical response observed was accompanied by an improvement in cardiac function as well as a decrease in inotropic support.[8] These results highlight both the interaction between age and TTE as well as the influence of age on thyroid hormone response to critical illness. Specifically, nongenomic T_3 mechanisms are immediate, occurring at the cell membrane, while genomic mechanisms necessitate T_3 transport intracellularly and binding to nuclear receptors with subsequent

modulation of gene transcription and protein translation. Prior studies have demonstrated that T_3 rapidly initiates transcription of genes in infants.[11] However, the results of this activity may not be clinically apparent for hours to days. That being said, the lack of statistically significant shorter TTE in the T_3-treated children older than 5 months (TTE was slightly prolonged in the $>$ 5-month-old T_3 treatment group) may reflect the dominance of nongenomic action relative to genomic action, particularly since most patients older than 5 months were extubated by 24 hours.[36]

The potential mechanism(s) underlying the positive thyroid hormone action in young infants in the TRICC trial was investigated by Olson and colleagues. Specifically, the investigators utilized a translational model to test the hypothesis that T_3 modulates pyruvate entry into the citric acid cycle (CAC), providing the energy support for improved cardiac function after ischemia-reperfusion (I/R) injury from CPB. They utilized three groups of piglets, administering intracoronary [(2-^{13}carbon [^{13}C]) pyruvate to all of them: (1) control group, (2) I/R group, and (3) I/R group that received T_3 during reperfusion (I/R-Tr). Compared with the I/R group, the I/R-Tr group increased cardiac power and oxygen consumption after I/R. Further, T_3 promoted a fourfold increase in anaplerotic carboxylation (PC) and oxidative pyruvate decarboxylation (PDC) fluxes into the CAC, providing potential substrate for elevated cardiac function after reperfusion.[37] The same group published a subsequent study further investigating the effects of T_3 supplementation on the CAC under extracorporeal membrane oxygenation (ECMO). They found that T_3-treated piglets on ECMO demonstrated enhanced lactate metabolism to the CAC, suggesting that T_3 disinhibits pyruvate dehydrogenase (PDH), thereby manipulating substrate utilization. Based on these findings, they concluded that T_3 supplementation to be a potential therapeutic option to facilitate weaning from mechanical circulatory support warranted further investigation.[38] The group went on to investigate this question by inducing cardiac injury in four groups of neonatal piglets with subsequent ECMO cannulation. As expected, the benefits of unloading the myocardium with ECMO, both functional and metabolic, were lost during the weaning period. T_3 supplementation during ECMO restored function, increased PDH flux into the CAC, and preserved adenosine triphosphate (ATP) stores. Specifically, T_3-treated piglets demonstrated significantly higher left ventricular systolic pressure and cardiac power during reloading with the ECMO weaning process compared with their untreated counterparts. Further, the ATP concentration was higher, and the absolute quantities of lactate and pyruvate were lower in the T_3-treated piglets.[39]

After elucidating the effect of T_3 supplementation on pyruvate oxidation during ECMO weaning, the same group investigated the effect of thyroid hormone on fatty acid (FA) metabolism while weaning from ECMO after cardiac surgery. Similar to the prior studies discussed, the T_3-treated group exhibited significantly better myocardial function. Specifically, they had lower left ventricular end-diastolic pressures and significantly higher cardiac output (% of baseline), cardiac power (% of baseline), and cardiac efficiency (%). Additionally, protein expression levels of phosphor-ACC, phospho-AMPKα, and phosphor-PDH, major proteins involved in the regulation of FA metabolism, were not significantly different among the three groups of piglets (control group, I/R group, I/R-Tr). In other words, T_3 supplementation, (similar to the prior study) reversed some of the I/R-induced impairments in substrate metabolism. It appears to do this by increasing relative flux through PDH without significant disturbance of FA metabolism. In conclusion, T_3 supplementation facilitates weaning from ECMO in this immature pig model.[38]

Thyroid Hormone Administration to Brain-Dead Organ Donors

The available data on the hormonal changes that occur between the time of brain death and organ procurement in organ donors are scant and contradictory. The changes in many thyroid parameters during brain death are unpredictable except for T_3, which has been reliably documented to be reduced in multiple observational studies.[40] However, the associations between thyroid hormone changes and both donor hemodynamics as well as ultimate organ quality are inconsistent.[41,42] Despite the lack of evidence, thyroid hormone administration is a management tool incorporated into the United Network for Organ Sharing (UNOS) Critical Pathway for the Organ Donor.[43] A systematic review by Macdonald and colleagues was recently published to examine the strength of the evidence in support of the use of thyroid hormone administration to brain-dead donors and to identify "high risk" donors who might potentially benefit from thyroid hormone therapy. Based on this review, there is low-level evidence to support routine administration of thyroid hormone in the brain-dead potential organ donor. Specifically, meta-analysis of four placebo-controlled randomized controlled trials showed no significant effect of thyroid hormone administration on donor cardiac index (pooled mean difference, 0.15 L/min/m^2; 95% CI: −0.18 to 0.48). However, this review focused on the adult organ donor population. Further, the percentage of donors who were hemodynamically unstable or clinically marginal due to various reasons was too small to adequately assess for a benefit of thyroid hormone administration in this subgroup.[9] Thus, further investigation of this topic within the pediatric organ donor population, particularly the high risk donors, is still needed.

Treatment for Nonthyroidal Illness Syndrome

The question of whether to treat abnormalities in circulating thyroid hormone levels in the absence of primary thyroid disease during systemic illness remains difficult to definitively answer on the basis of currently available data. As mentioned in the introduction, multiple explanations for these aberrancies have been discussed.[4] Furthermore, it is possible that benefit from thyroid hormone replacement exists only in specific settings such as inciting events, severity of illness, ages, etc.

Consideration for thyroid hormone replacement or supplementation should include assessment of benefit versus risk. Thyroid hormone is known to increase basal metabolic rate. Therefore, subclinical thyrotoxicosis as a result of T_3 supplementation could, theoretically, lead to increased heart rate, ectopic atrial beats and/or dysrhythmias, increased cardiac contractility, and systemic ventricular mass and diastolic dysfunction.[44] Fortunately, the safety profile of T_4 treatment has been well established in the adult and pediatric cardiac population.[7,45,46] Substantial safety data, originating from adults undergoing coronary artery bypass grafting, challenge the theoretical risks of arrhythmia induction by T_4 supplementation. In fact, multiple studies showed either no statistical differences or significant improvements in hemodynamic variables, incidence of arrhythmias, episodes of ischemia, or inotropic drug requirements between those treated with either oral or intravenous T_3 versus no treatment.[46–53] T_3 therapy has been found to be equally safe in preterm infants, infants, and children with no significant side effects.[7,35,45,54–59] T_3 therapy was discontinued prematurely in two neonates undergoing aortic arch reconstruction secondary to an incidence of ectopic atrial tachycardia and an incidence of systemic hypertension.[60] However, no adverse events were associated with thyroid hormone supplementation.[8] Thus, the data overwhelmingly suggest that T_3 supplementation is safe among diverse adult and pediatric populations with critical illness.[61] Because of abnormalities in T_4 to T_3 conversion in these critical illnesses, a role for T_4 supplementation does not appear to exist.

Future studies are needed to determine efficacy of T_3 repletion in critically ill children with low thyroid syndromes. These studies will face considerable design and enrollment challenges considering the inherent heterogeneity in many disease populations. The TRICC trial, the largest randomized clinical trial performed, attempted to deal with diverse complexity in cardiac disease by diagnostic stratification. Logistics of performing multicenter stratification in a randomized clinical trial are extremely complex. Furthermore, the U.S Food and Drug administration is hesitant to review data obtained by post hoc analyses, such as the TRICC determination that patients younger than 5 months benefited from T_3 supplementation. In following, the U.S. Food and Drug Administration (FDA) funded the current ongoing multicenter TRICC-2 trial, which will specifically evaluate safety and clinical efficacy for T_3 supplementation in patients younger than 5 months (Clinical Trials.gov, NCT02320669). Other studies of specific populations may also be warranted. For instance, a study in Indonesia has demonstrated that oral T_4 supplementation can also be used to treat sick euthyroid syndrome.[62] Clinical trials to determine efficacy for oral T_4 in relatively sick and malnourished Indonesian children undergoing CPB are now underway (ClinicalTrials.gov, NCT02222532). These large clinical trials will hopefully determine efficacy of thyroid hormone supplementation in these critically ill infants and children.

Once the safety of treatment has been established, the efficacy should become the focus in deciding whether to treat. As discussed previously, multiple studies have demonstrated treatment benefit in specific subpopulations of children with critical nonthyroidal illness. Taken together, the demonstrated association between low thyroid hormone levels and poor clinical outcomes, the beneficial effects of thyroid hormone supplementation in multiple critically ill subpopulations, and the well-established safety profile of T_3 therapy, thyroid hormone supplementation in the pediatric ICU is reasonable.

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